Results: Out of 108 patients treated with radio (chemo) therapy, 76 patients had HPV 16 positivity, 24 HPV 16 & 18, 1 patient HPV 18 while 6 patients were HPV 16 & 18 negative. The mean HPV 16 and HPV 18 viral load was $9.3x10^6$ copies/10ng DNA and $1.3x10^6$ copies/10 ng DNA respectively. At 5 months post treatment, 96 patients had complete response, 9 had residual/ recurrent local disease and 3 had distant relapse. There was significant reduction in HPV viral load at treatment completion, 2 and 5 months post treatment in complete responders (p
Conclusions: A significant reduction in HPV 16 and 18 viral load occurs in complete responders after completion of radical radio (chemo) therapy. However, further correlation between persistence or re-infection of HPV and local recurrence is ongoing in this prospective study.

OC-0493

Head and neck cancer HPV16 variant analysis, HPV E2 variations and E2 protein disruption as radiation sensitivity biomarker

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Purpose/Objective: Head and neck squamous cell carcinoma (HNSCC) associated with HPV has improved response to radiation therapy compared to HPV non-associated SCC. However, despite this, examples of local failures within HNSCC are beginning to emerge. This work aims to understand and describe risk factors to radiation resistance and increased virulence. HPV-16 non-European (NE) variants have been shown to have an 11-fold increased association with cervical cancer diagnosis than the European (E) variants.
Materials and Methods: Our initial analysis of 43 HPV-16 positive human tumors with PCR that E variants were more likely associated with higher stage and lymph node positive disease. E2 sequencing was completed for a subset of HPV 16 variants and analized. The presence of intact E2 DNA has shown improved local control and a trend for improved disease free survival, for head and neck cancer and cervical cancer respectively. To test this, we evaluated five head and neck SCC cell lines for presence of intact E2 DNA and mRNA using E2 PCR primers. Clonogenic survival assays were completed and colony formation was determined.
Results: E variants were detected more often in higher stage HNSCC (79% stage IV v 57% stage I-III, p=0.160) and were also more prevalent in node positive disease (82% v 53%, p=0.074). Additional tumor HPV 16 variant sequencing needs to be completed to more statistical power to detect differences in virulence and presentation of malignancy. The subset of cancer tissue variant E2 sequencing revealed variation within areas know to bind p53 and may affect apoptosis. H&N cancer cell line E2 DNA and mRNA expression was confirmed and results reveal that E2 disrupted or absent cell lines were significantly more radioresistant than their counterparts.
Conclusions: Preliminary evidence suggests that HPV 16 variants may be a important factor in evaluation and risk stratification. In addition, E2 may serve as a useful tool to determine which patients harbor tumors that are radioresistant in HPV-positive HNSCC and has implications for tumor specific cancer treatments.

Joint Symposium: ESTRO-ASTRO: Novel treatment approaches for oligometastasis

SP-0494

Survival after SBRT of colo-rectal carcinoma oligometastases

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It is a general belief that patients with oliometastases benefit from local ablation of the metastases. Large retrospective cohort studies have shown favorable survival outcome after surgical resection and radiofrequency ablation. Stereotactic body radiation therapy (SBRT) is increasingly used for this purpose. Unfortunately, the evidence for the use of SBRT of metastases is limited to relatively small retrospective studies often with patients with various histological types. Colorectal carcinoma (CRC) metastasis are often treated with surgery and RFA and it is one of the indication where we have the best published experience with SBRT.
A large cohort of CRC patients with metastases primarily in the lungs and liver treated with SBRT was published recently (1). This study demonstrated promising survival rates of 77, 33 and 15% at 1, 3 and 5 years after SBRT in a cohort of patients who had already received other treatments for metastatic disease. Multivariate analysis revealed that WHO performance status (0-1) solitary metastasis and small size of metastasis (≤ 30 mm) were significantly related to favorable survival. The survival of metastatic CRC did not significantly differ from the survival of non-CRC metastases patients treated with SBRT and the analysis did not identify any tumor type with a more favorable outcome when metastases were treated with SBRT.
In general, the approach to metastatic CRC has become more aggressive. A number of specialties offer therapies for patients with liver oligo-metastases and a multidisciplinary team approach in the management of these patients is highly important. SBRT may be utilized for a group of patients who cannot be treated with surgery.
There is sufficient data demonstration that SBRT can be used in therapy of CRC metastases, but there is a great need for randomized clinical trials to prove the efficacy of SBRT in treatment of oligo-metastases and for trials to explore the need for systemic therapy along with SBRT.
Reference:

1. Mette Marie Fode, Morten Høyer: Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases, Radiother Oncol *In press* 2015

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Liver metastases and SBRT

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As a common deposit for tumor cells, the liver is second only to the lymph nodes as a site of metastatic disease. The liver is also the most common site of metastatic disease in cancers of the large intestine because it is the first major organ reached by venous blood draining from the intestinal tract.
Unfortunately, by the time some patients present with liver metastases there is usually evidence of the extensive systemic spread of the disease, and patients can no longer be considered as candidates for surgery or other local ablative treatments. However, there is a subset of patients with a few metastases (oligometastases) in which the role of a radical local treatment such as stereotactic body radiation therapy (SBRT) could change disease progression (1).
Most patients with liver metastases have a well-preserved liver function with absence of underlying diseases. Prediction of hepatic toxicity after SBRT in these patients have been primarily based on the assumption of a parallel architecture where subvolumes of the organ function relatively independently and a fraction of the organ can be damaged without clinical effect. A complication is only observed if more than a critical volume is damaged (2). A critical volume of 700 ml of healthy liver (liver-GTV) receiving a total dose of less than 15Gy in 3 fractions has been broadly adopted to avoid hepatic toxicity (3).
An accurate correlation between imaging and pathology is essential for target definition in SBRT. A good agreement between macroscopic pathology and MR imaging has been found for a group of colorectal liver metastases, suggesting that MR can be used for accurate tumor delineation (4). Pilot studies have reported positive integration of 4D PET-CT in the target delineation of liver metastases.
The liver moves with respiration, and can change position depending of filling in adjacent anatomical structures. Assessment of motion of tumor or tumor surrogates (fiducial markers) is mandatory for liver SBRT (5). Management of breathing motion during planning and/or treatment (abdominal compression, active breathing control, gating, tumor tracking) and image guided techniques for daily repositioning are required to increase treatment accuracy, and make possible to deliver very high doses to the tumor while protecting the surrounding organs at risk.
High local control rates after SBRT for liver metastases have been reported in several phase I-II and retrospective trials showing a local control between 80% and 100% at 2 years (6-8).
The American Association for Physics in Medicine has organized an SBRT working group (WGSBRT) to assess tumor control probability (TCP) and normal tissue control probability (NTCP) values for SBRT applied to different organs. In the case of liver metastases, the working liver TCP group investigated if outcomes were affected by the dose regimen. Local control outcomes were significantly better at 3 years for BED >100Gy_{10}.
Toxicity reported after SBRT for liver metastases is in general limited. Quality of life has been assessed after liver SBRT showing no significant change between baseline and 1, 3, and 6 months after treatment (9).
Conclusion: High precision SBRT is an effective technique for treatment of liver oligometastases. Using the right dose, excellent local control rates can be achieved with limited toxicity and without impairment of quality of life.

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Disease specific evidence for the treatment of oligometastases: beyond colon cancer

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The treatment strategies for many metastatic cancers are undergoing a dramatic paradigm shift. Systemic therapies are increasingly tailored to unique characteristics of individual tumors. Routine testing for genetic mutations and rearrangements are identifying patients who can benefit from “targeted” therapies. Histology driven chemotherapy is commonly being used. The advent of highly active immune modulating therapies have altered treatment strategies for many diseases that once had few good systemic options.
Simultaneously, there is a growing belief that the number and location of metastases should also be considered in addition to molecular, histology, or immune related factors.
Patients with metastases limited in number and destination organ, *oligometastases*, are often considered for surgery and/or radiation due to reports of long disease free intervals following treatment of all known metastases. Across many diseases, it is common to see 20-25% of patients treated for limited metastatic disease alive and disease free years later. Systemic therapies are often reserved for patients with more widespread or “polymetastases”.
Breast cancer patients often present with limited metastases. Approximately 50% of patients treated on clinical trials had 2-4 sites of disease at enrollment. Additionally, breast cancer patients with limited metastases have improved survival compared to those with more extensive metastases. Following treatment of all known metastases median survivals are numerically higher than historic populations. Therefore, NRG BR002 is randomizing patients with 1-2 breast cancer metastases to ablative therapy (surgery or radiation) plus standard of care therapy vs standard of care therapy alone.
Oligometastases are also common in NSCLC. A prospective phase II study demonstrated long term survivors in patients treated with radiotherapy or surgery for oligometaststic disease. Multiple randomized studies have been attempted in this population to test consolidation with radiation following systemic therapy as well as radiation integrated into a systemic therapy treatment platform, however both have failed to accrue. An increasingly useful strategy in